Application No.: 10/019,376

Office Action Dated: September 17, 2004

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1. (currently amended) A compound of formula

$$Q = \begin{bmatrix} R^1 \\ A^2 \\ A^4 \end{bmatrix} \begin{bmatrix} A^2 \\ A^3 \end{bmatrix} \qquad (I)$$

an ester or amide prodrug, N-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof

wherein
$$-a^1=a^2-a^3=a^4$$
- represents a bivalent radical of formula
-CH=CH-CH=CH- (a-1);

wherein each hydrogen atom in the radical (a-1) may optionally be replaced by halo, $C_{1\text{-}6}$ alkyl, nitro, amino, hydroxy, $C_{1\text{-}6}$ alkyloxy, polyhalo $C_{1\text{-}6}$ alkyl, carboxyl, amino $C_{1\text{-}6}$ alkyl, mono- or di($C_{1\text{-}4}$ alkyl)amino $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyloxycarbonyl, hydroxy $C_{1\text{-}6}$ alkyl, or a radical of formula

wherein =Z is =O, =CH-C(=O)-NR 5a R 5b , =CH₂, =CH-C₁₋₆alkyl, =N-OH or =N-O-C₁₋₆alkyl;

Q is a radical of formula

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$Y^1$$
 $CH-X^1$
 Y^1
 $CH-X^1$
 Y^1
 $CH-X^1$
 Y^1
 $N-X^2$
 $(CH_2)_v$
 $(b-5)$
 $(b-6)$
 $(b-7)$
 $(b-8)$

wherein

Alk is C_{1-6} alkanediyl;

Y¹ is a bivalent radical of formula –NR²- or –CH(NR²R⁴)-;

X¹ is NR⁴, S, S(=O), S(=O)₂, O, CH₂, C(=O), C(=CH₂), CH(OH), CH(CH₃), CH(OCH₃), CH(SCH₃), CH(NR^{5a}R^{5b}), CH₂-NR⁴ or NR⁴-CH₂;

 X^2 is a direct bond, CH₂, C(=O), NR⁴, C₁₋₄alkylene-NR⁴, or NR⁴-C₁₋₄alkylene;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3 ; with the proviso that when R^3 is hydroxy or C_{1-6} alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10} alkanediyl optionally substituted with one, two or three substituents selected from hydroxy, C_{1-6} alkyloxy, aryl C_{1-6} alkyloxy, aryl C_{1-6} alkylthio, aryl C_{1-6} alkylthio, arylcarbonyl, HO(-CH₂-CH₂-O)_n-, C_{1-6} alkyloxy(-CH₂-CH₂-O)_n-, aryl C_{1-6} alkyloxy(-CH₂-CH₂-O)_n-, amino, mono-or di(C_{1-6} alkyloxycarbonylamino and aryl;

R¹ is a bicyclic heterocycle selected from quinolinyl, **isoquinolinyl**, quinoxalinyl, benzofuranyl, benzothienyl, benzimidázolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthyridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl or a radical of formula

DOCKET NO.: JANS-0028 (JAB-1500 US)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$(CH_{2})_{m} \qquad (CH_{2})_{m} \qquad (CH_$$

and said bicyclic heterocycles may optionally be substituted in either of the two cycles with 1 or where possible more substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;

each R^2 independently is hydrogen, formyl, C_{1-6} alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7} cycloalkyl substituted with $N(R^6)_2$, or C_{1-10} alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7} cycloalkyl, C_{2-5} alkanediyl, piperidinyl, mono-or di $(C_{1-6}$ alkyl)amino, C_{1-6} alkyloxycarbonylamino, aryl and aryloxy;

 R^3 is hydrogen, hydroxy, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyloxy, aryl $C_{1\text{-}6}$ alkyloxy;

R⁴ is hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C₁₋₆alkyl; or

DOCKET NO.: JANS-0028 (JAB-1500 US)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

 R^{5a} and R^{5b} , or R^{5c} and R^{5d} taken together form a bivalent radical of formula -(CH₂)_s- wherein s is 4 or 5;

 R^6 is hydrogen, C_{1-4} alkyl, formyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more substituents selected from halo, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, polyhalo C_{1-6} alkyl, and C_{1-6} alkyloxy; and Het is pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl.

2. (cancelled)

- 3. (previously presented) A compound according to claim 1, wherein Q is a radical of formula (b-5) wherein v is 2 and Y^1 is $-NR^2$.
- 4. (previously presented) A compound according to claim 1, wherein R^2 is C_{1-10} alkyl substituted with NHR⁶.
- 5. (currently amended) A compound according to claim 1, wherein G is a direct bond or C₁₋₁₀alkanediyl optionally substituted with one, two or three substituents selected from the group consisting of hydroxy, C₁₋₆alkyloxy, arylC₁₋₆alkyloxy, HO(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, and arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n-.
- 6. (currently amended) A compound-according to claim 1, wherein the compound is $(\pm)-N-[1-(2-\text{aminoethyl})-4-\text{piperidinyl}]-4-\text{methyl}-1-[1-(8-\text{quinolinyl})\text{ethyl}]-1H-benzimidazol-2-amine monohydrate;$
 - (\pm) -N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-bromo-5,6,7,8-
 - $tetrahydro-8-quinolinyl)-{\it 1H-} benzimidazol-2-amine\ trihydrochloride\ trihydrate;$
 - (\pm) -N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-4-methyl-IH-benzimidazol-2-amine;

Application No.: 10/019,376

Office Action Dated: September 17, 2004

- (\pm) -N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-IH-benzimidazol-2-amine trihydrochloride trihydrate; (\pm) -N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(1-methyl-IH-benzimidazol-4-yl)methyl]-IH-benzimidazol-2-amine;
- (\pm)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(ethoxy-8-quinolinylmethyl)-1H-benzimidazol-2-amine;
- (\pm) -N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(5,6,7,8-tetrahydro-5-quinoxalinyl)-1H-benzimidazol-2-amine;
- N-[1-(2-aminoethyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-IH-benzimidazol-2-amine;
- N-[1-(8-quinolinylmethyl)-1H-benzimidazol-2-yl]-1,3-propanediamine trihydrochloride monohydrate;
- (\pm)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-1H-benzimidazol-2-amine trihydrochloride dihydrate;
- $(\pm)-N-[1-[1-(aminomethyl)-2-methylpropyl]-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-1H-benzimidazol-2-amine;$
- (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(1-isoquinolinylmethyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
- N-[1-(2-aminoethyl)-4-piperidinyl]-1-(5,6,7,8-tetrahydro-5-quinoxalinyl)-1H-benzimidazol-2-amine trihydrochloride trihydrate;
- (\pm)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-1H-benzimidazol-2-amine;
- (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
- (\pm)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-(5,6,7,8-tetrahydro-2,3-dimethyl-5-quinoxalinyl)-IH-benzimidazol-2-amine trihydrochloride trihydrate;
- (\pm)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-1H-benzimidazol-2-amine;

DOCKET NO.: JANS-0028 (JAB-1500 US)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

- (\pm)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(3-chloro-5,6,7,8-
- $tetrahydro-5-quinoxalinyl)-{\it 1H-} benzimidazol-2-amine\ trihydrochloride\ monohydrate;$
 - (\pm) -N-[1-(2-aminoethyl)-4-piperidinyl]-1-(3-chloro-5,6,7,8-tetrahydro-5-
- quinoxalinyl)-4-methyl-1H-benzimidazol-2-amine trihydrochloride dihydrate;
- (\pm) -N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-
- quinolinylmethyl]-4-methyl-1H-benzimidazol-2-amine monohydrate;
- (\pm)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(1-methyl-1H-benzimidazol-4-yl)methyl]-1H-benzimidazol-2-amine;
- (\pm) -N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-1H-benzimidazol-2-amine;

((1-isoquinolin-1-ylmethyl)-1H-benzoimidazol-2-yl)-piperidin-4-yl-amine; (1-(4-(1-isoquinolin-1-ylmethyl-1H-benzoimidazol-2-ylamino)-piperidin-1-ylmethyl)-2-methyl-propyl)-carbamic acid tert-butyl ester; or

an ester or amide prodrug, N-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof.

- 7. (previously presented) A method of treating a respiratory syncytial viral infection, comprising the step of administering a therapeutically effective amount of a compound as claimed in any one of claims 1 and 3 to 6.
- 8. *(previously presented)* A pharmaceutical composition, comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 and 3 to 6.
- 9. (previously presented) A process of preparing a composition as claimed in claim 8, comprising the step of intimately mixing said carrier with said compound.
- 10. (original) An intermediate of formula

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$P - Q_1 - N - a_1 - a_3 - (IV)$$

with R^1 , G and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, P being a protective group, and Q_1 being defined as Q according to claim 1 but being devoided of the R^2 or R^6 substituent.

PATENT

11. (original) An intermediate of formula

$$(O =)Q_3 - (IX)$$

with R^1 , G and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and $(O=)Q_3$ being a carbonyl derivative of Q, said Q being defined according to claim 1, provided that it is devoided of the NR^2R^4 or NR^2 substituent.

12. (original) An intermediate of formula

$$Q \xrightarrow{N} a^{1} a^{2} a^{2}$$

$$Q \xrightarrow{N} a^{4} a^{3} a^{3}$$
(XXII)

with R^1 , Q and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and (O=)G₂ being a carbonyl derivative of G, said G being defined according to claim 1.

13. (currently amended) A process of preparing a compound as claimed in claim 1, comprising at least one step selected from the group consisting of:

Application No.: 10/019,376

Office Action Dated: September 17, 2004

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)

PATENT

with R^1 , G, Q and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

b) deprotecting an intermediate of formula (IV)

$$P = Q_1 = \begin{bmatrix} R^1 \\ N \\ A^4 \end{bmatrix} \begin{bmatrix} a^2 \\ A^4 \end{bmatrix} \begin{bmatrix} A^1 \\ A^4 \end{bmatrix} \begin{bmatrix} A^1 \\ A^4 \end{bmatrix} \begin{bmatrix} A^2 \\ A^3 \end{bmatrix}$$
(IV)
(I-a)

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, H-Q₁ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

c) deprotecting and reducing an intermediate of formula (IV-a)

DOCKET NO.: JANS-0028 (JAB-1500 US)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$P \longrightarrow Q_{1a}(CH=CH) \longrightarrow N \longrightarrow A^{a_1 \\ a_2 \\ (IV-a)} \longrightarrow H \longrightarrow Q_1 \longrightarrow N \longrightarrow A^{a_1 \\ a_2 \\ (I-a)} \longrightarrow H \longrightarrow Q_1 \longrightarrow N \longrightarrow A^{a_1 \\ a_2 \\ a_3 \longrightarrow A^{a_1 \\ a_3 \longrightarrow A^{a_1 \\ a_4 \longrightarrow A^$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, H-Q₁ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, $Q_{1a}(CH=CH)$ being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group;

d) deprotecting an intermediate of formula (V)

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

e) deprotecting an intermediate of formula (VI)

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

f) deprotecting an intermediate of formula (VII) or (VIII)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$P = Q_{1'}(OP) = A_{1} A_{2} A_{3}$$

$$(VII) \qquad (I-a-2)$$

$$P = Q_{2'}(OP) = A_{1} A_{2} A_{3}$$

$$(VIII) \qquad (I-a-1-1)$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ defined as in claim 1, H-Q₁·(OH) being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, H₂N-Q₂·(OH) being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

g) amination of an intermediate of formula (IX)

$$(O \Longrightarrow) Q_3 \xrightarrow{N} A_{a^4} A_{a^3} A_{a^4} A_{a^5} A_{a^$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ defined as in claim 1, and H_2N-Q_3H being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6 , or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

Application No.: 10/019,376

Office Action Dated: September 17, 2004

h) reducing an intermediate of formula (X)

PATENT

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

i) reducing an intermediate of formula (X-a)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$NC - Q_4 \xrightarrow{R^{1} - C_{1-6}alkyl - OH} A_{a^4} \xrightarrow{a^2} \frac{reduction}{ammonia/C_{1-6}alkylOH} \qquad H_2N - H_2C - Q_4 \xrightarrow{N} A_{a^4} A_{a^3} \qquad (I-a-1-3-1)$$

with G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, and R^1 being defined as R^1 according to claim 1 provided that it comprises at least one substituent, in the presence of a suitable reducing agent and suitable solvent;

j) amination of an intermediate of formula (XI)

$$CH_{2}-Q_{4}$$

$$N$$

$$A_{1}$$

$$A_{2}$$

$$A_{3}$$

$$A_{4}$$

$$A_{3}$$

$$A_{4}$$

$$A_{3}$$

$$A_{4}$$

$$A_{3}$$

$$A_{4}$$

$$A_{4}$$

$$A_{3}$$

$$A_{4}$$

$$A$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and H_2N - CH_2 -CHOH- CH_2 - Q_4 being defined as Q according to claim 1 provided that Q comprises a CH_2 -CHOH- CH_2 - NH_2 moiety, in the presence of a suitable amination reagent;

k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia

$$C_{1-4}\text{alkyl} - C_{1-4}\text{constant} = C_{1-4}\text{alkyl} - C_{1-4}\text{alkyl} - C_{1-4}\text{alkyl} = C_{1-4}\text{alkyl} - C_{1-4}\text{alkyl} = C_{1-4}$$

Application No.: 10/019,376

Office Action Dated: September 17, 2004

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and H-C(=O)-Q₁ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is formyl;

PATENT

l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)

$$(O=)Q_{5} \xrightarrow{N \qquad a_{1} \qquad a_{2} \qquad anination} R^{2a} - NH - HQ_{5} \xrightarrow{N \qquad a_{1} \qquad a_{2} \qquad a} (I-c)$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and R^{2a} -NH-HQ₅ being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by R^{2a} , R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent;

m) reducing an intermediate of formula (XV)

$$(R^{6})_{2}N_{-}(C_{1}\text{-9alkyl})\text{-NH}\text{-HQ}_{5} \\ N \\ C(=O)OC_{1}\text{-4alkyl} \\ (XV)$$

$$R^{1}$$

$$a^{1} \\ a^{2}$$

$$A^{2}$$

$$A^{2}$$

$$A^{3}$$

$$A^{2}$$

$$A^{3}$$

$$A^{2}$$

$$A^{3}$$

$$A^{4}$$

$$A^{3}$$

$$A^{2}$$

$$A^{3}$$

$$A^{4}$$

$$A^{4}$$

$$A^{3}$$

$$A^{4}$$

$$A^{4$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ defined as in claim 1, and $(R^6)_2N$ -[$(C_{1-9}alkyl)CH_2OH$]-NH-HQ₅ being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by $C_{1-10}alkyl$ substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a suitable reducing agent;

n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$P = Q_{1} \longrightarrow \begin{pmatrix} A & O & P \end{pmatrix}_{w}$$

$$P = Q_{1} \longrightarrow \begin{pmatrix} A & A & A \\ A & A & A \\ A & A & A \end{pmatrix}$$

$$(XVI)$$

$$(I-d)$$

$$P = Q_{1} \longrightarrow \begin{pmatrix} A & A & A \\ A & A & A \\ A & A & A \end{pmatrix}$$

$$(XVI-a)$$

$$(I-d-1)$$

$$P = Q_{1} \longrightarrow \begin{pmatrix} A & A & A \\ A & A & A \\ A & A & A \end{pmatrix}$$

$$(XVI-a)$$

$$(I-d-1)$$

$$Q = \begin{pmatrix} A & A & A \\ A & A & A \\ A & A & A \end{pmatrix}$$

$$(I-d-1)$$

$$Q = \begin{pmatrix} A & A & A \\ A & A & A \\ A & A & A \end{pmatrix}$$

$$(I-d-2)$$

with G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and H-Q₁ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and R^{1a} -(A-O-H)_w, $R^{1a'}$ -(A-O-H)₂ and $R^{1a''}$ -(A-O-H)₃ being defined as R^1 according to claim 1 provided that R^1 is substituted with hydroxy, hydroxyC₁₋₆alkyl, or HO(-CH₂-CH₂-O)_n-, with w being an integer from 1 to 4 and P or P₁ being a suitable protecting group, with a suitable acid- $\frac{1}{2}$

o) amination of an intermediate of formula (XVII)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$C_{1^{-4}alkyl} - O - C_{-Alk} - X^{1} - N - Alk - X^{1} - Alk -$$

with R^1 , G, $-a^1=a^2-a^3=a^4$ -, Alk, X^1 R^2 and R^4 defined as in claim 1, in the presence of a suitable amination agent;

PATENT

p) amination of an intermediate of formula (XIX)

$$H = C + C_{1-3} \text{alkyl} + NR^4 + N$$

with R^1 , G, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and Q_6N - CH_2 - C_{1-3} alkyl- NR^4 being defined as Q according to claim 1 provided that in the definition of Q, X^2 is C_{2-4} alkyl- NR^4 , in the presence of a suitable amination agent;

q) deprotecting an intermediate of formula (XXI)

with R^1 , Q, and $-a^1=a^2-a^3=a^4$ - defined as in claim 1, and HO-G₁ being defined as G according to claim 1 provided that G is substituted with hydroxy or HO-(CH₂CH₂O-)_n; and

r) reducing an intermediate of formula (XXII)

Application No.: 10/019,376

Office Action Dated: September 17, 2004

$$Q = \bigvee_{N = a^{1} = a^{2} = a^{2}}^{R^{1}} \qquad \text{reduction}$$

$$Q = \bigvee_{N = a^{1} = a^{2} = a^{2}$$

PATENT

with R^1 , Q, and $-a^1=a^2-a^3=a^4$ defined as in claim 1, and H-G₂-OH being defined as G according to claim 1 provided that G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, in the presence of a suitable reducing agent.

14. (cancelled)

15. (cancelled)

- 16. (previously presented) The process of claim 13, further comprising the step of converting compound of formula (I'), stereochemically isomeric forms, metal complexes, quaternary amines or N-oxide forms thereof, into a therapeutically active non-toxic acid addition salt by treatment with an acid.
- 17. (previously presented) The process of claim 13, further comprising the step of converting compound of formula (I'), stereochemically isomeric forms, metal complexes, quaternary amines or N-oxide forms thereof, into a therapeutically active non-toxic base addition salt by treatment with alkali.
- 18. (previously presented) The process of claim 13, further comprising the step of converting the acid addition salt form of compound of formula (I'), stereochemically isomeric forms, metal complexes, quaternary amines or N-oxide forms thereof, into the free base by treatment with alkali.

Application No.: 10/019,376
Office Action Dated: September 17, 2004

The process of claim 13, further comprising the step of 19. (previously presented) converting the base addition salt form of compound of formula (I'), stereochemically isomeric forms, metal complexes, quaternary amines or N-oxide forms thereof, into the free acid by treatment with acid.

PATENT